REMARKS

This Amendment is in response to the Examiner's Final Office Action mailed on September 23, 2005 and Applicants' telephone interviews with Examiner Bradley L. Sisson on January 24, 30 and 31, 2006. Claims 1-26 and 28 are canceled. Claim 27 is currently amended. Claims 27, 29 and 30 are now pending.

Reconsideration is respectfully requested in view of the above amendments to the claims and the following remarks.

I. Interviews with Examiners

Applicants express appreciation to Examiner Sisson for conducting telephone interviews with Applicants on January 24, 30 and 31, 2006. During the interviews Applicants discussed the issues raised by the Examiner in the Office Action mailed September 23, 2005, details of which are described in the following sections.

II. Objection to Specification

The Examiner has objected to the specification as documents have been improperly incorporated by reference. Applicants amend the specification by deleting the paragraph on page 20, line 14: "All references mentioned above are incorporated in their entirety by references." Withdrawal of the objection is therefore respectfully requested.

III. Claim Objections

Claim 28 stands rejected under 37 CFR 1.75(c) as being of improper dependent form and for failing to further limit the subject matter of a previous claim. Applicants' cancellation of claim 28 renders the rejection moot.

IV. Claim Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 27 and 28 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement because according to claim 28 no digoxigenin-labeled probe recited in claim 27 is used. Applicants' cancellation of claim 28 renders the rejection moot.

IV. Claim Rejections under 35 U.S.C. § 103(a)

1. Over Parker et al. in view of Gelmetti et al.and Bargmann et al.

Claims 27-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,565,323 (Parker et al.) in view of Gelmetti et al. (1998) J. Virol. Methods 72:219-226 (Gelmetti et al.) and US Patent No. 4,935,341 (Bargmann et al.).

Independent claim 27 as amended specifies an in situ-hybridization (ISH) method for detecting a single copy of the Her-2/neu gene in chromosomal DNA in an intact cell in a tissue sample by using a digoxigenin-labeled Her-2/neu probe and brightfield microscopy.

As discussed during the interview on January 24, 2006 and acknowledged by the Examiner in the Office Action on page 6, section 8, Parker et al. discloses hybridization of probes to DNA immobilized on membranes (column 16, lines 38-55; and thus fails to teach or suggest *in situ* hybridization.

As discussed during the interview on January 24, 2006, Gelmetti et al. teaches away from the claimed invention of detecting a single copy of the Her-2/neu gene in chromosomal DNA in the nucleus of a cell. Gelmetti et al. discloses detection of rabbit haemorrhagic disease virus (RHDV) in the **cytoplasm** of hepatocytes. Page 22, 2nd column, 3rd paragraph. According to Gelmetti et al., the positive signals generated by the antisense RNA probe were "confined to the hepatocyte cytoplasm" and the "[n]uclei showed no reactivity." Thus, Gelmetti et al. does not teach detection of a gene in chromosomal DNA, let alone teach or suggest detection of **a single copy of the Her-2/neu gene in chromosomal DNA in the nucleus of a cell.**

The third reference, Bargmann et al., fails to supply the claim elements missing in Parker et al. and Gelmetti et al. In fact, Bargmann et al. teaches away from the claimed invention of detecting a single copy of the Her-2/neu gene using brightfield microscopy. Bargmann et al. discloses **radio-labeled DNA probe** for detecting mutation of the Her-2/neu gene in a Southern hybridization assay. Thus, Bargmann et al. does not teach detection of the Her-2/neu gene using a brightfield microscopy, let alone teach or suggest detection of **a single copy** of the Her-2/neu gene in **chromosomal DNA** in the **nucleus of a cell**.

In view of the failure of the cited references to teach or suggest the claimed invention, a prima facie case of obviousness has not been established under 35 U.D.S. §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

2. Over Vernole et al. and Davison et al.

During the interview on January 30, 2006, the Examiner brought to Applicants' attention two references, Vernole et al. (1990) BioTechniques 9:200-204 (cited in Applicants' IDS filed on June 13, 2005); and Davison et al. (1998) Am. J. Pathol. 153:1401-1409 (cited in Applicants' IDS filed on October 10, 2002).

As discussed during the interview, Applicants pointed out that Vernole et al. does not discloses the claimed invention of detection of a single copy of the Her-2/neu gene in a tissue sample. Applicants are the first to demonstrate successful detection of a single copy of the Her-2/neu gene in a tissue sample (such as breast tumor tissue specimens described in Examples 1 and 2) by using the method specified in the claims,

In contrast, Vernole et al. merely shows detection of single-copy genes in **cells isolated from cell cultures and spread onto slides** before the hybridization assay. Page 200, column 3, the paragraph under "Chromosome Preparations." Vernole et al. does not teach or suggest detection of the Her-2/neu gene, nor **a single copy of a gene in a tissue sample**, let alone teach or suggest how to detect a single copy of the Her-2/neu gene in a tissue sample. In fact, as discussed during the interview, for a hybridization assay of cells isolated and spread on a slide as shown in Vernole et al. it is much easier for the nucleic acid probes to get access to the chromosomal DNA than to that hidden in cells buried in a tissue. Vernole et al. neither teaches detection of a single copy of the Her-2/neu gene, nor teaches how to detect a single copy of the Her-2/neu gene in a cell buried in a tissue sample.

Davison et al. fails to fill in the gap left by Vernole et al. As pointed out by Applicants during the interview, Davison et al.'s disclosure is further away from Vernole et al. since Davison et al. utilized fluorescent microscopy to detect hybridization signals in the samples. *See* page 1403, column 2. It is well recognized in the art that as in ISH assays using radio-labeled probes it is much easier to detect signals by fluorescent microscopy except for disadvantages such as health hazards

and fast fading of the fluorescent markers. See the specification of the instant application at page 3, lines 13-26. Davison et al. neither teaches nor suggests the problems associated with fluorescent microscopy nor provides a solution to the problems by disclosing how to detect a single copy of a gene in a tissue sample using brightfield microscopy.

In view of the failure of Vernole et al. and Davison et al. to teach or suggest the claimed invention, a prima facie case of obviousness has not been established under 35 U.D.S. §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

3. Over Morey et al.

Prior to the interview on January 31, 2006, the Examiner faxed to Applicants a new reference, Morey et al. (1992) J. Clin. Pathol. 45:673-678.

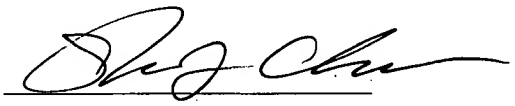
During the interview on January 31, 2006, Applicants pointed out that similar to Gelmetti et al., Morey et al. discloses detection of virus-infected cells in tissues. *See* Abstract. As described and shown in Figure 1, positive hybridization signals are detected in "acellular material within blood vessels as well as with individual infected cells" throughout fetal lung tissues. Thus, Morey et al.'s assay involves detection of viral signals at "low resolutions." This reference does not teach detection of a gene in chromosomal DNA, let alone teach or suggest detection of a single copy of the Her-2/neu gene in a tissue sample.

In view of the failure of Morey et al. to teach or suggest the claimed invention, a prima facie case of obviousness has not been established under 35 U.D.S. §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

CONCLUSION

Applicants believe that they are entitled to a letters patent and respectfully solicit the Examiner to expedite prosecution of this patent to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: February 21, 2006 By: 

Shirley Chen, Ph.D.
Reg. No. 44,608

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Dial: (650) 565-3856
Fax: (650) 493-6811
Customer No. 21971